subject to adequate peer review as recommended by the Risk Assessment Advisory Committee [RAAC, 1996] and consistent with Executive Order W-137-96. Consequently, health risks from perchlorate were not evaluated in the assessment.

2.8 SUMMARY OF PERCHLORATE CONTAMINATION-RELATED EVENTS WITHIN THE UNITED STATES

Perchlorate contamination at numerous facilities throughout the country has been known. However, perchlorate contamination now appears more widespread based upon improved analytical methods with much lower detection limits. Perchlorate contamination exists near Las Vegas, where the Colorado River and Lake Mead have been found to contain levels of perchlorate ranging from 4 to 16 µg/L. Colorado River and Lake Mead serve as drinking water sources for approximately 12 million people. In addition, numerous drinking water supply wells in California have been shut down due to excessive perchlorate contamination. As a result, research and development associated with perchlorate is proceeding at a rapid pace. Investigations are currently being performed to address laboratory analytical methods, toxicological effects, and water treatment technologies.

The efforts are being spearheaded by a group recently formed called the Interagency Perchlorate Steering Committee (IPSC). The IPSC is comprised of 15 members who are listed in Table 2-1. On May 19-21, 1998, the IPSC sponsored a three day meeting called the Perchlorate Stakeholders Forum in Henderson, Nevada to present the status of ongoing and planned efforts regarding perchlorate issues. Summary papers on many critical issues were handed out in advance of the meeting (provided in Appendix B). The information presented in the Perchlorate Stakeholders Forum summaries and presentations is discussed in this report. Table 2-2 presents a timeline of events relative to perchlorate contamination and cleanup.

In 1993, a group was formed called the Perchlorate Study Group (PSG) that consists of the major solid rocket manufacturers, including CSD, and ammonium perchlorate manufacturers. The PSG has provided $800,000 in financing for toxicological studies that are in progress. The Department of Defense, primarily the Air Force, has also contributed approximately 1.4 million dollars for the toxicological studies. The PSG has hired a consulting organization, Toxicology Excellence for Risk Assessment (TERA), to coordinate perchlorate toxicology studies and risk assessment issues.

Several web sites have been developed to assist in providing information on perchlorate-related issues. California DHS, TERA, and the American Water Works Association Research Foundation (AWWARF) have web sites at the addresses listed below. The EPA plans to establish a web site for perchlorate issues in the near future.

7/14/98
Kevin - Interesting summary of perchlorate from a UTC (San Jose) report done for the water board I am looking at. Your copy
MK

TABLE 2-1
INTERAGENCY PERCHLORATE STEERING COMMITTEE

EXECUTIVE COMMITTEE
Peter Grevatt (USEPA-OSWER)
Kevin Mayer (USEPA-IX)
Lt. Col. Dan Roger (DOD-USAF)
Annie Jarabek (USEPA-NCEA)
Mike Osinski (EPA-OW)

HEALTH EFFECTS/TOXICITY
Dave Mattie (DOD-USAF)
Annie Jarabek (USEPA-NCEA)

TREATMENT TECHNOLOGY
Ed Urbansky (USEPA-NRMRL)
Wayne Praskins (USEPA-IX)
Jim Hurley (DOD-USAF)

ECOLOGICAL IMPACTS (T/T)
Mark Sprenger (USEPA-OERR)
Cornell Long (DOD-USAF)

ANALYTICAL
Captain Dave Tsui (DOD-USAF)
Steve Pia (USEPA - NERL)
Howard Okamoto (Cal-DHS)
Sanwat Chaudhuri (Utah DEQ)

PEER REVIEW
Peter Grevatt (USEPA-OSWER)

SELECTED WEB SITES WITH PERCHLORATE INFORMATION

Provider	Web Site
California DHS Division of Drinking Water and Environmental Management	www.dhs.cahwnet.gov/org/ps/ddwem/ddwemindex.htm
TERA	www.tera.org
AWWARF	www.awwarf.com

2.9 ONGOING TOXICOLOGICAL RESEARCH ON PERCHLORATE HEALTH RISKS

A summary paper of perchlorate health effects, toxicology, and studies in progress, was presented at the Perchlorate Stakeholders Forum in Henderson, Nevada on May 19 through 21, 1998. This summary paper is presented in Figure 2-2 and provides information on ongoing research on perchlorate toxicology.

TABLE 2-2
TIMELINE OF PERCHLORATE-RELATED EVENTS

1953	Ammonium perchlorate manufacturing begins in Henderson, Nevada.
1959	CSD begins operations at Coyote Center Site in San Jose, California.
1992	USEPA issues provisional reference dose (RfD) for perchlorate.
1993	Aerojet began investigation of perchlorate treatment technologies.
1993	Perchlorate Study Group (PSG) formed.
1994	Aerojet performed first ion exchange pilot-scale studies.
1995	USEPA issues revised provisional RfD for perchlorate.
1996	Aerojet performed first biodegradation pilot-scale studies.
10/96	Aerojet Cleanup & Abatement Order issued requiring perchlorate treatment.
1/97	Perchlorate detected in Sacramento drinking water supply wells.
3/97	First perchlorate RfD peer review performed by TERA (funded by PSG).
3/97	California DHS develops ion chromatography (IC) analytical method having reporting limit of 4 μg/L.
5/97	Toxicological data gaps on perchlorate identified by external peer review panel and required new studies identified.
6/97	Metropolitan Water District (MWD) detects perchlorate contamination in Lake Havasu, which leads to detections in Colorado River and Lake Mead.
6/97	California DHS issues provisional action level for perchlorate in drinking water.
1997	Perchlorate detected at many locations and in numerous drinking water supplies in California and Nevada including Lake Mead and the Colorado River.
11/97	New toxicological studies began on perchlorate.
1/98	CSD initiates sampling of creeks using new analytical method (IC).
1/98	Interagency Perchlorate Steering Committee (IPSC) formed.
5/98	AWWARF treatment technology study bids received.
5/98	Perchlorate Stakeholders Forum meeting held in Henderson, Nevada.
6/98	Southwest Focused Groundwater Conference held in Anaheim, California.
8/98	AWWARF treatment technology projects to begin.
9/98	Ion exchange pilot-scale studies sponsored by Main San Gabriel Watermaster to be completed.
10/98	Internal peer review of toxicological studies and revised RfD to be completed.
10/98	Aerojet's full-scale biodegradation system scheduled for completion.
11/98	External peer review of toxicological studies and revised RfD to be completed.
5/99	Aerojet 500-1000 gpm biodegradation pilot-plant scheduled for start-up.
8/99	Phase I of AWWARF treatment technology projects to be completed.

FIGURE 2-2. HEALTH EFFECTS AND TOXICOLOGY OF PERCHLORATE

PERCHLORATE CONTAMINATION IN THE ENVIRONMENT

Health Effects / Toxicology of Perchlorate

Introduction

A significant portion of the expedited research underway to address perchlorate contamination in the environment has been dedicated to obtaining a reliable and comprehensive data base on the health effects and toxicology of perchlorate. Such robust data are necessary to develop a health risk assessment that includes an estimate called a reference dose (RfD) which can be used to evaluate the potential risk of human exposures. The RfD can also be used in risk management programs to help guide the range where analytical methods must be effective and to target treatment technologies. The health effects data serve as the lynchpin in the overall integrated approach to addressing the emerging issues of perchlorate contamination.

Background

The currently available database on the health effects and toxicology of perchlorate or its salts is very limited. The majority of human data are clinical reports of patients treated with potassium perchlorate for hyperthyroidism resulting from an autoimmune condition known as Graves' disease. Potassium perchlorate is still used diagnostically to test thyroid hormone [thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4)] production in some clinical settings. The basis for the effect on thyroid hormone function is the competitive inhibition of iodide anion uptake into the thyroid gland by perchlorate anion (ClO_4^-) which then results in reduced thyroid hormone production.

It is difficult to establish a dose-response for the effects on thyroid function from daily or repeated exposures in normal humans from the data on patients with Graves' disease because of a variety of confounding factors, including: the effect of the disease, that often only a single exposure and not repeated exposures were tested, that only one or two doses were employed, and that often the only effect monitored was iodine release from the thyroid or control of the hyperthyroid state. There are limited data in normal human subjects and laboratory animals that support the effect of perchlorate on thyroid hormones, but the majority of these additional studies suffer from the same limitations with respect to the number of doses and exposures. These limitations prevent establishment of a quantitative dose-response estimate for the effects on thyroid hormones after long-term repeated exposures to perchlorate in healthy human subjects.

The typical objective of a health risk assessment is to evaluate a comprehensive array of testing endpoints that represent various life stages in which potential effects could occur, e.g., the developing fetus through adult and for effects on reproductive capability. Thyroid hormone deficiencies, such as those induced by perchlorate, can affect normal metabolism, growth and development. No robust data exist to evaluate other potential target tissues or effects. There are no data to evaluate the effects of perchlorate in potentially susceptible population such as

developing fetuses, nor are there data on the effects of perchlorate on reproductive capacity of male or female laboratory animals.

Benign tumors have been reported in the thyroids of male Wistar rats and female BALB/c mice treated with repeated, high dose exposures (2 years at 1,339 and 46 weeks at 2,147 mg/Kg-day, respectively) of potassium perchlorate in drinking water. Benign tumors in the thyroid have been established to be the result of a series of progressive changes that occur in the thyroid in response to interference with thyroid-pituitary homeostasis (i.e., perturbation of the normal stable state of the hormones and functions shared between these two related glands). This progression is similar regardless of the cause of the thyroid hormone interference (Hill et al., 1989; Capen, 1997; Hurley et al., submitted). The EPA has adopted the policy that an assumption of a threshold based on these precursor lesions along the progression is appropriate for the dose-response of chemicals which cause this type of disruption in the thyroid when they do not have genotoxic activity, i.e., cause damage to DNA or show other genetic disruption (U.S. EPA, 1998). Therefore, a dose-response estimate established using the no-observed-adverse-effect level for the precursor lesions should be an estimate also protective for potential benign tumor development. Existing shorter-term studies indicate that perchlorate causes changes in the thyroid typical of the progression described and genotoxic studies are underway to establish that perchlorate does not have any activity relevant to carcinogenicity.

Provisional Health Risk Assessment

The EPA Superfund Technical Support Center issued a provisional reference dose (RfD) in 1992 and a revised provisional RfD in 1995. An RfD is calculated as an estimate of a daily oral human exposure that will result in no deleterious noncancer effects over a lifetime. Ideally, an RfD is based on a database that evaluates an array of endpoints that address potential toxicity during various critical lifestages, from developing fetus through adult and reproductive stages. The provisional RfD values (1992 and 1995) were based on an acute study in which single doses of potassium perchlorate caused the release of iodide from the thyroids of patients with Graves' Disease. The no-observed-adverse-effect-level (NOAEL) was determined to be 0.14 mg/Kg-day based on release of iodine in the thyroid followed by incomplete inhibition of iodine uptake. Uncertainty factors that ranged from 300 to 1000 were applied to account for data missing on additional endpoints and extrapolations required to calculate a lifetime human exposure level. Standard assumptions for ingestion rate and body weight were then applied to the RfD to calculate the reported range in the ground water cleanup guidance levels of 4 -18 parts per billion (ppb). The California Department of Health Services (CA DHS) adopted 18 ppb as its provisional action level.

The provisional RfD values issued are listed by the EPA only as provisional because they did not undergo the internal Agency and external peer review required of estimates available on the EPA's Integrated Risk Information System (IRIS). The outcome of an external peer review convened in March 1997 of an analogous RfD derivation by an independent organization, Toxicology Excellence for Risk Assessment (TERA), was the determination that the health effects and toxicity data were insufficient for a credible quantitative risk analysis. The external peer review panel concluded that the data were not sufficient to rule out effects of perchlorate on other organs, so that it could not be determined unequivocally that the effects on the thyroid were the critical effect. In particular, the reviewers were concerned that developmental toxicity,

notably neurological development due to hypothyroidism during pregnancy, could be a critical effect of perchlorate that has not been adequately examined in studies to date.

New Health Effects / Toxicology Studies Underway

In response to the March 1997 external peer review of the provisional RfD value, a subsequent external peer review of experts was convened in May 1997 to recommend and prioritize a set of studies to address the key data gaps and reduce uncertainties in various extrapolations. The objective of the new studies is to provide a comprehensive database that provides for development of a robust RfD estimate that reduces the uncertainties inherent in the provisional values. Funding for the studies was procured and obligated through a variety of sources, principally the USAF and the Perchlorate Study Group (PSG).[1] The protocols for the studies were reviewed by external peer reviewers from the EPA, California EPA, academia, industry, private institutes and Health Canada. The timeframe for the development of these new data has been precedent setting and has been a direct result of a unique partnering initiative. Typical research and development mechanisms would have required a number of years to accomplish these same studies.

Eight new studies were recommended in order to provide a comprehensive array of endpoints. These are described below along with their anticipated role in informing the revised health risk assessment.

(1) 90-Day Subchronic Oral Bioassay Study. This study is considered the minimum data requirement for derivation of an oral RfD. The study will identify other target tissues, test young adult rats, and also provide data on the effect of repeated exposure to perchlorate on thyroid hormone levels. These data may also allow reduction of the uncertainty factor applied for database deficiencies.

(2) Neurobehavioral Developmental Study. This study will evaluate the potential for developmental neurotoxicity of perchlorate by assessing functional and morphological endpoints in offspring from mother exposed during pregnancy and lactation. Neurotoxicity endpoints may be a critical effect and the developing organism a sensitive subpopulation. These data may allow reduction of the uncertainty factors applied for intrahuman variability and database deficiencies.

(3) Segment II Developmental Study. This study will evaluate the potential for perchlorate to cause birth defects in rabbits and will identify a potentially critical effect and subpopulation. This study will also provide data on the thyroid hormone effects in a second species (in addition to rats). These data may allow reduction of the uncertainty factor applied for database deficiencies.

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[1]The PSG is a consortium of defense contractors and manufacturers including: Alliant Techsystems, American Pacific/Western Electrochemical Company, Atlantic Research Corporation, Lockheed Martin, Thiokol Propulsion Group, and United Technologies Chemical Systems. – AEROJET ALSO

FIGURE 2-2. (Continued)

(4) Two-Generation Reproductive Toxicity Study. This study will evaluate the potential for perchlorate to cause deficits in reproductive performance in adult rats and for toxicity in the young offspring. This study may identify a potentially critical effect and allow for reduction of the uncertainty factor applied for database deficiencies.

(5) ADME (Absorption, Distribution, Metabolism, and Elimination) Studies. These studies will be performed to understand the pharmacokinetics (how perchlorate is absorbed, distributed, metabolized and excreted) of perchlorate in test animals and humans. These data will provide information that will allow construction of quantitative extrapolation of dose across species (e.g., rat to human).

(6) Perchlorate Mechanism Studies. These studies will be conducted by a comparison of the existing literature and of new *in vitro* and *in vivo* data that evaluate the effects of perchlorate on the iodide uptake mechanism across species to aid in the quantitative extrapolation of dose.

(7) Genotoxicity Assays. These studies will evaluate the potential for carcinogenicity by evaluating mutations and toxic effects on DNA. These data will be useful to evaluate whether the benign thyroid tumors are likely to be a result of the proposed threshold pathogenesis process.

(8) Immunotoxicity Studies. These studies will evaluate the potential for perchlorate to disrupt immune function and identify a potentially critical effect. These data may help to reduce the uncertainty factor applied for database deficiencies.

Additional work may be required to mathematically model the dosimetry (pharmacokinetics) and toxic effects in order to increase the accuracy of a health risk determination, but this will need to be evaluated as the new data become available. An epidemiological study has been proposed to look at infant thyroid hormone data from mothers who were exposed in their drinking water supplies. The analysis would rely on the dose reconstruction data to the level of either a city or census block and will assume either that all women who lived in that area were exposed to that level of perchlorate or impose standard assumptions from other such studies (e.g., 20% of women drink bottled water). The dose reconstruction of what was in the water would have to be constructed on occurrence data once the hydrology in the aquifers and transport and transformation processes can be worked out. Both of these studies are considered refinements to the revision of the RfD that will likely result from the new studies.

EPA Plans for Revised Health Assessment and Peer Review

Revised Health Risk Assessment

The National Center for Environmental Assessment (NCEA) in the Office of Research and Development (ORD) of the EPA plans to evaluate the health effects and toxicology data from these new studies and then issue a new assessment at the end of September 1998. The new assessment, all the new data, and the study protocols will then be subjected to an external peer

FIGURE 2-2. (Continued)

review in October 1998 before the assessment is finalized. The assessment, data, and protocols will be available to the public at the time of release to external peer review.

Once finalized, this new peer-reviewed health assessment and new oral RfD will serve as a more robust health effects estimate than the existing provisional values with which to evaluate exposure estimates in order to characterize potential risk from perchlorate contamination or with which to develop guidance levels for cleanup and to target treatment technologies.

External Peer Review of Revised Assessment

Independent, external peer review of the study protocols, toxicity studies, and revised reference dose and health assessment for perchlorate will be critical to ensuring that future decisions based on the RfD will be protective of human health. EPA's Office of Solid Waste and Emergency Response (OSWER) will task a qualified contractor to manage peer review of technical issues related to the development of the reference dose, including study design, conduct of toxicity studies, statistical treatment of data, selection of critical effect, selection of uncertainty factors and risk characterization. The peer review will be conducted by a panel of technical experts in developmental toxicology, reproductive toxicology, genetic toxicology, general toxicology, pathology, biostatistics, dose-response modeling and risk assessment. Peer reviewers will be selected from a pool of candidates nominated by stakeholders in the perchlorate issues. The RfD assessment package, supporting studies, and study protocols for the new data will be distributed to the peer review panel in advance of the peer review meeting. Peer reviewers will independently review the RfD assessment package and supporting studies, and will submit their written comments to OSWER's contractor prior to the peer review meeting. The peer reviewer's comments will be compiled by OSWER's contractor and will be distributed to all of the peer reviewers and the public in advance of the meeting. The peer reviewers will gather for a two day meeting in a location selected based on accessibility to stakeholders and the peer reviewers. The public will be invited to attend and observe the peer review meeting. Following the peer review meeting, the peer review panel will generate a report detailing their comments on the reference dose package and supporting studies. EPA NCEA will generate a responsiveness summary report which will discuss in detail how they will address the comments raised by the peer reviewers. The provisional reference dose will subsequently be issued by EPA.

Questions for Discussion

1. What are the effects of hypothyroidism in adults versus infants?

2. What relevance do these effects have to children's health?

3. What are the potential impacts to pregnant women who drink contaminated water?

4. How will new information on health effects be used in the future?

This discussion paper was prepared for an Interagency Perchlorate Steering Committee stakeholder forum, May 19-21, 1998, and does not represent any of the participating agencies' policy.

FIGURE 2-2. (Continued)

References

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